REMARKS

Status of the Claims

Claims 2, 4-10, 24-43, 49-60, 63-66, 68-75 are pending. Claims 69, 71 and 73 are indicated as allowed and Claims 6 and 75 are indicated to be allowable.

35 U.S.C. § 112, 1st paragraph, Written Description

The Advisory Action mailed December 15, 2006 reiterated the rejection of claims 2, 4, 7-10, 24-43, 49-60 and 63-66 as allegedly not described by the specification as filed for the reasons of record. (Advisory Action page 2). The particular arguments addressed in the Advisory Action related to the Office's continued insistence that the claims embrace Gag polypeptides having activities other than immunogenicity and that there is nothing in the record indicated hat modifying a Gag-encoding sequence as claimed was known to the skilled artisan.

(a) The Rejection Continues to be Premised on Improper Claim Construction

In response to Applicants' statements that the polypeptide encoded by the claimed sequences is not required to have Gag activities other than eliciting a Gag specific immune response is sufficient, the Advisory Action states "...the claimed product also embraces a functional Gag polypeptide. There is nothing in the claim that excludes an HIV Gag polypeptide, wherein the polypeptide does possess an activity of a functional Gag protein." (Advisory Action, page 2).

However, there is only one activity that the Gag polypeptide encoded by the claimed molecules must exhibit and that is immunogenic activity. It is irrelevant whether the polypeptide does or does not exhibit other Gag activities. Indeed, as repeatedly noted immunogenic function was well known at the time of filing to be separable from "other" Gag functions. *See, e.g.,* WO 00/39302 (Ref FX-1 of IDS filed December 18, 2002 and considered February 13, 2003).

To assert that the term "immunogenic HIV Gag polypeptide" is not defined and/or does not limit the scope of the claims on the grounds that other Gag activities are not expressly excluded stretches the meaning of the claims beyond credulity. The skilled artisan would clearly

recognize that an "immunogenic HIV Gag polypeptide" is one that elicits a Gag-specific immune response.

(b) Description of Known Molecules

Applicants also wish to clarify that the citation of *Falkner v. Inglis* for the proposition that known molecules need not be re-described to satisfy 35 U.S.C. § 112, 1st paragraph was made with respect to the Gag polypeptides encoded by the claimed polynucleotides, not with regard to the clearly novel polynucleotides themselves. In other words, as the Examiner acknowledges, the claimed modified polynucleotides were not known in the art, but the Gag polypeptides they encode were known. Accordingly, in the instant case, Applicants are not required to re-describe the sequences of known immunogenic HIV Gag polypeptides as encoded by their polynucleotides in order to satisfy the written description requirement. The claims are directed to novel polynucleotides that encode immunogenic HIV Gag polypeptides. At the time of filing (and indeed to this day), the structure (primary and secondary) of immunogenic HIV Gag polypeptides was well-known to the skilled artisan.

(c) Possession of the Genus is not Determined by the Amount of Testing Required

The Examiner also continues to assert that the skilled artisan would not know how to determine sequences that encode an HIV Gag polypeptide on the grounds that many variants would have to be tested and that the possibility of such testing does not evince possession. (Advisory Action, page 2).

The Examiner's assertion that testing establishes that the specification lacks an adequate written description is legally and factually erroneous.

Legally, the amount or nature of any "testing" is not a factor considered in assessing the adequacy of description. *See, e.g., Capon v. Eshhar,* 76 USPQ2d 1078, 1085-1086 (Fed. Cir. 2005):

> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. ...

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. [citations omitted].
>
> It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See In re Angstadt, 537 F.2d 498, 504 [190 USPQ 214] (CCPA 1976) ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. Both Eshhar and Capon present not only general teachings of how to select and recombine the DNA, but also specific examples of the production of specified chimeric genes.
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> The PTO points out that for biochemical processes relating to gene modification, protein expression, and immune response, success is not assured. However, generic inventions are not thereby invalid.

As repeatedly noted, and admitted by the Examiner in dismissing the relevance of *Capon,* a written description inquiry is highly fact-dependent. The facts in this case establish Applicants have provided more than adequate guidance for obtaining the claimed polynucleotides, including "testing" of any number of different sequences. With respect to the alleged large number of variants that must be tested, Applicants note that the skilled artisan would know, well prior to testing, that many of these sequences would not encode polypeptides (*e.g.,* if they contain a stop codon near the start site).

Regardless of the number of variants, Applicants reiterate that the as-filed specification teaches, in detail and with working examples, how to obtain the claimed polynucleotides. Each and every member of the claimed genus – be it 2 or 2 billion members in size – is **literally** described in the as-filed specification. Satisfaction of the written description requirement does not necessitate that each and every member of the claimed genus be set forth, let alone "tested" in order to show possession. Nor does the written description requirement necessitate a showing that the skilled artisan can predict *a priori* each and every nucleotide sequence falling within the scope of the claims. Even if it did, Applicants have met this inasmuch as the as-filed

specification contains unambiguous **literal** description of the structure of any member of the claimed genus by reference to its sequence similarity to a reference sequence.

Thus, the process for "testing" the polypeptides encoded by the claimed sequences is much more than possible, it is amply described in sufficient detail to demonstrate that Applicants were in possession, at time of filing, of any nucleotide sequence that exhibits 90% identity to SEQ ID NOs:3 or 4 and which encodes an HIV Gag polypeptide that elicits an Gag-specific immune response in a subject.

(d) Reduction to Practice is Not Required to Satisfy the Written Description Requirement

The Examiner also again alleged that actual reduction to practice of a single (or few) species is not sufficient in the present case to establish possession because of the alleged "lack of sufficient guidance for how to make the claimed genus." (Advisory Action, page 2).

For the reasons of record and reiterated herein, the Examiner also errs in this assertion. The specification contains ample guidance in this regard. Description of a single species can provide an adequate description, even for a broad genus. Description does not require exemplification. *See, Capon v. Eshhar* 76 USPQ2d 1078 (CA FC 2005):

> It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 [190 USPQ 214] (CCPA 1976) ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. ...

See, also, Falkner v. Inglis, in which the Federal Circuit cited *Capon* in reiterating that actual reduction to practice is not required (*Falkner,* at 1007-1008):

> Specifically, we hold, in accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description **(2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent**; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. ...

> As we explained in *Capon v. Eshhar*, "[t]he 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." 418 F.3d 1349, 1357 [76 USPQ2d 1078] (Fed. Cir. 2005). ....
>
> Thus, to the extent that written description requires a showing of "possession of the invention," *Capon*, 418 F.3d at 1357 (emphasis added), [it is] clear that **an invention can be "complete" even where an actual reduction to practice is absent.**

These are clear, fact-independent holdings of the Federal Circuit. Thus, a specification need not describe every polynucleotide permutation in order for an inventor to obtain a generic claim and actual reduction to practice of polynucleotides falling within the scope of the claims is never necessary for compliance with the written description requirement.[1]

In any event, the as-filed specification has in fact exemplified that sequences comprising the claimed reference sequence that encode immunogenic HIV Gag polypeptides. In fact, the exact sequence of reference sequences SEQ ID NOs:3 and 4 are literally described in the as-filed specification, it is clear that Applicants were in possession of not only these molecules but, in addition, nucleotides exhibiting 90% identity to these molecules.

The as-filed specification establishes skilled artisan can envision the detailed structure of every single member of the claimed genus (a polynucleotide exhibiting 90% identity to the recited reference sequence). The specification describes, in detail, how HIV Gag polypeptides are identified, for example by Western blotting, ELISA or the like and how to determine immunogenicity. (See, *e.g.*, Examples).

Further, contrary to the Examiner's assertion, the sequences (including "critical" epitopes) of various HIV Gag-encoding polynucleotides (as well as Gag polypeptides themselves) were known at the time of filing and are described, for example, in the Background section and references cited therein.

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[1] *See, also*, the PTO Guidelines, favorably commented on by the Federal Circuit, include various Examples that establish that claims to a genus of sequences are properly described if (1) the DNA sequence is novel, (2) unobvious, and (3) a specific activity is recited. *See,* Examples 9 and 14 of the PTO Guidelines on Written Description, reproduced in the Response filed September 26, 2005.

The test for determining satisfaction of the requirement of Section 112, 1st paragraph is not what sequences are actually reduced to practice in the as-filed specification, but, rather, what the disclosure as a whole and available knowledge to determine whether the specification as-filed evinces possession of the claimed subject matter to the skilled artisan. The skilled artisan, having followed the teaching of the specification, would have no doubts that Applicants were in possession of the claimed subject matter (and that the as-filed specification teaches how to make and use the claimed sequences).

Therefore, for the reasons of record and those set forth herein, the as-filed specification more than satisfies the written description requirement of 35 U.S.C. § 112, 1st paragraph.

35 U.S.C. § 112, 1st Paragraph, Enablement

As set forth in the seminal case of *In re Marzocchi,* 439 F.2d, 220, 223, 169 USPQ 367, 369 (CCPA 1971), a patent application is presumptively enabled when filed:

> [a]s a matter of Patent Office practice ... a specification .. must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Moreover,

> it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 369-370. Indeed, as pointed in the Patent Office's own Training Manual on Enablement (1993, citing *In re Wright,* 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection."

In the pending case, the Examiner has supported the enablement rejection by citing Freed, Baker, Attwood, Gerhold, Russel, Wells and Ngo, which were alleged to demonstrate the unpredictability of polynucleotides encoding polypeptides exhibiting "the biological function of a wild-type Gag polypeptide." (Advisory Action, page 2, citing previous Office Actions). However, these references do not provide a properly reasoned and supported basis for finding non-enablement.

Freed, which allegedly demonstrates that a Gag protein has "numerous" and "complex" roles, is not germane to the claims as pending. The polynucleotides of the claims are not required to have all Gag activities. Rather, all that is required is that the polynucleotides exhibit the requisite identity to the references sequences and encode a polypeptide that elicits a Gag-specific immune response. As noted above and throughout prosecution, the specification at issue provides ample guidance in this regard, for example, on page 14 and references cited therein. Accordingly, Freed is not relevant to the pending claims.

Baker, Attwood, Russell and Ngo are cited for allegedly showing unpredictability of the relationship of primary, secondary and tertiary structure of a polypeptide. However, as noted above, a Gag-specific immune response can be generated by short epitopes and, accordingly, there is no need to predict, a priori, the "structure" or "folding" of a polypeptide encoded by the claimed molecules.

Likewise, Gerhold and Wells relate to methods of determining gene function based on EST sequence. This is not relevant to the pending claims, in which the only function required by the polypeptide is that elicits a Gag-specific immune response and which required function does not necessitate the entire coding sequence or core structures.

The relevant question regarding enablement remains what the specification and state of the art at the time of filing teaches one of skill in the art in regard to eliciting Gag-specific immune responses. The disclosures of Freed, Baker, Attwood, Gerhold, Russel, Wells and Ngo do not change the fact that any experimentation needed to polynucleotides exhibiting 90% sequence identity to SEQ ID NOs:3 and 4 and which encode an immunogenic Gag polypeptide is utterly routine in view of the teachings of the specification and the state of the art. The Office has not provided sufficient evidence supporting non-enablement and, in the absence of necessary

relevant evidence contradicting the teachings of the specification and state of the art, the rejection cannot be maintained.

(a) Undue Experimentation is Not Required to Make and Use the Claimed Polynucleotides

Applicants remind the Office that it is well settled that even time-consuming or expensive experimentation is **not** undue if it is routine. (See, *e.g.*, PTO Training Manual on Enablement, pages 30-31, citing *United States v. Telectonics Inc.*, USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* 490 U.S. 1046 (1989) holding the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000). Furthermore, the notion that one of ordinary skill in the art must have reasonable assurance of obtaining an active claimed product has been emphatically rejected by the courts. *See, Angstadt* at 219. So long as it is clear that some species render a composition operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1, of 35 U.S.C. §112. *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988.

In the instant case, the specification discloses the precise sequence of the reference sequences, how to determine sequences having 90% identity to these reference sequences, how to express a polypeptide from the polynucleotides having the requisite sequence homology, and The actual scope of the claims, and the nature of the guidance provided in the specification (*e.g.*, at Examples 2-7 and Sections 2.1.3 and 2.3), along with the conventional nature of methods of modifying sequences and determining their function, all establish that the specification as filed fully enables the claims.

Moreover, the clear teachings of the specification are supplemented by further evidence of the routine nature of making and using the claimed polynucleotides. In particular, as noted above, WO 00/39302 (Ref FX-1 of IDS filed December 18, 2002 and considered February 13, 2003, now U.S. Patent No. 6,602,705, which demonstrates that synthetic polynucleotides similar to those claimed (but for Type B HIV) encode immunogenic Gag polypeptides. Applicants are not required to show perfect efficiency or success rates. All that is required is that one of skill in

the art could make and use the claimed polynucleotides. The specification and evidence of record plainly demonstrate that this requirement has been met.

In sum, given the clear teachings in the specification and the high level of knowledge at the time of filing, it would not require undue experimentation to make and use polynucleotides as claimed. Furthermore, for the reasons of record and reiterated above, the references cited by the Office do not provide any reasons to doubt that the skilled artisan could make and use the claimed molecules.

Declaratory Evidence Relevant to Both Enablement and Written Description Has Not Been Properly Considered

As noted above and previously, the Declarations of Drs. Donnelly and Ulmer, previously submitted on December 18, 2002 and January 20, 2004 (respectively) have not been adequately considered. In point of fact, these declarations further establish that the sequences having at least 90% identity to SEQ ID NO:3 or SEQ ID NO:4 are both enabled and described by the as-filed specification.

Drs. Donnelly and Ulmer attest to the fact that the specification enables one of one of skill in the art to make and use the claimed subject matter. *See,* Donnelly Declaration, ¶7 and ¶8 and Ulmer Declaration, ¶11 and ¶12).

With regard to written description of "core" or "essential regions", as previously noted and reiterated above, Dr. Ulmer establishes that immunogenicity does is not directly correlated with either primary or tertiary structure

Thus, using specific facts, Drs. Donnelly and Ulmer conclude that the as-filed specification describes and enables the claimed subject matter. This convincing, factual evidence has been improperly dismissed by the Office (*see, e.g., In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

Thus, for the reasons of record and above, the specification describes and enables the claimed subject matter. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is in condition for allowance. If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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